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Citation for published version:
McKechanie, A, Barnicoat, A, Trender-Gerhard, I, Allison, M & Stanfield, A 2019, 'Fragile X-associated conditions: Implications for the whole family', *British Journal of General Practice*, vol. 69, no. 686, pp. 460-461. https://doi.org/10.3399/bjgp19X705425

Digital Object Identifier (DOI):
10.3399/bjgp19X705425

Link:
Link to publication record in Edinburgh Research Explorer

Document Version:
Publisher's PDF, also known as Version of record

Published In:
British Journal of General Practice

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Download date: 07. May. 2023

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Fragile X-associated conditions:

implications for the whole family

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Submitted: 22 January 2019; **Editor's response:** 18 February 2019; **final acceptance:** 20 March 2019.

©British Journal of General Practice 2019; 69: 460–461.

DOI: https://doi.org/10.3399/bjgp19X705425

INTRODUCTION

Fragile X syndrome (FXS) is a triplet-repeat expansion disorder of the X chromosome, with repeats of more than 200 (sometimes referred to as the full mutation) causing FXS and ~59–200 repeats (the so-called premutation) being responsible for a variety of clinical presentations. Clinicians in primary care should be aware of these conditions and in particular be vigilant for common comorbidities to allow for early treatment. This article summarises the common issues for individuals with FXS and carriers of the premutation.

HOW ARE INDIVIDUALS WITH FRAGILE X SYNDROME TYPICALLY AFFECTED?

FXS is the most common inherited cause of intellectual disability, occurring in approximately 1 in 3000–4000 males and 1 in 6000–8000 females. Although the genetic underpinnings of FXS are similar across individuals, the manifestations vary widely and in some ways there is no 'typical' presentation. Nonetheless, males with the syndrome generally have an intellectual disability ranging from mild to severe, whereas females are much more variably affected (due to random X-inactivation) and can range from being essentially asymptomatic to having a severe intellectual disability. There are a number of common physical comorbidities associated with the syndrome including epilepsy (~25%), mitral valve prolapse (≤80%), hyperextensible joints, and an increased risk of inguinal hernias. Anxiety, attention deficit hyperactivity disorder (ADHD), and autism spectrum disorders (ASDs) are also significantly more common. Hyperarousal and sensory hypersensitivity are frequent symptoms, which may occur across a range of diagnoses. It is worth noting that, although one-third to two-thirds of individuals with FXS may meet criteria for an ASD, the presentation often varies subtly from that seen in idiopathic ASDs. In particular, some traits such as social difficulties and atypical eye contact may have very different underpinnings in FXS as compared with ASDs.[1]

WHAT INTERVENTIONS ARE RECOMMENDED IN FRAGILE X SYNDROME?

To date there is no medication specifically for core FXS symptoms (although this is an active area of clinical trial research). However, active vigilance in primary care is recommended for common comorbidities, which often impact quality of life most. Particularly, epilepsy, anxiety, and ADHD are common in individuals with FXS,[2] and active treatment for these should be considered. As ever, clinicians should be aware of the possibility of diagnostic overshadowing, meaning that treatable comorbidities may go untreated if attributed to core FXS symptomatology. The Royal College of General Practitioners' syndrome-specific medical health check guide for FXS provides further details on common comorbidities to be routinely reviewed in primary care.[3] Where necessary, referral to the local community learning disability team should be considered to support optimal diagnosis and treatment (Box 1). Multidisciplinary assessment is key, particularly occupational therapy for functional and sensory assessment, and speech and language therapy for communication support. Many families find the support of specific fragile X support organisations to be of help; the Fragile X Society (https://www.fragilex.org.uk/) being the UK-based organisation for this.

HOW ARE CARRIERS OF THE FMR1 PREMUTATION TYPICALLY AFFECTED?

The FMR1 premutation is carried by up to 1 in 150 females and 1 in 470 males. Historically, carriage of the FMR1 premutation (which is found in families with FXS) was not thought to be associated with any morbidity. However, more recently it has become apparent that it brings with it the increased likelihood of

Box 1. Genetic diagnosis in intellectual disability

- Seeking a genetic diagnosis for an intellectual disability is standard care in paediatric services, although there are large numbers (especially of adults) who have either never had genetic testing or for whom it was so long ago so as to be of limited meaning.
- It is estimated that routine genetic testing in individuals with intellectual disability can identify a genetic cause in up to 20%, with more detailed sequencing (not yet routinely available outside research studies) taking this up to over 50%.[4]
- Genetic testing should ideally be a routine part of care and should be considered where it has not been done previously. Clinicians should discuss with their local genetics department and community learning disability team to establish local practices.

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Acknowledgements

The authors are most grateful to the input from the McDonald family, former family in residence at the Patrick Wild Centre (http://patrickwildcentre.com/family-in-residence/), and the board of the Fragile X Society for their helpful input into, and comments on, the article. Their input helped to shape the article and hopefully make it of the greatest relevance to affected individuals and families, and their GPs.

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a number of conditions, notably including fragile X-associated premature ovarian insufficiency (FXPOI), fragile X-associated tremor and ataxia syndrome (FXTAS), and higher rates of mood and anxiety disorders.

Fragile X premature ovarian insufficiency (FXPOI) affects approximately 20% of female premutation carriers with increased infertility, and menopause occurring on average 5 years early.[5] A small proportion of women will experience the menopause at a much earlier stage, in their 20s or 30s. Notably, women with the full mutation do not, however, experience FXPOI.

Approximately 45% of males and ≤16% of females carrying an FMR1 premutation develop fragile X-associated tremor-ataxia syndrome (FXTAS). This neurodegenerative condition usually occurs over the age of 50 with risk of manifestation and severity increasing with age. Apart from the core symptoms of action tremor and/or ataxia (gait difficulties and disturbed limb coordination in particular), it may present with mild Parkinsonism, cognitive decline (short-term memory and executive function deficits), neuropathy, neuropathic pain, and autonomic dysfunction. Regarding the treatment of FXTAS, referral to neurology should be considered, where symptomatic treatments for action tremor, Parkinsonism, neuropathic pain, and mood/anxiety problems may have a role. One small trial of memantine for cognitive effects showed no effect, although there may be a role for cholinesterase inhibitors. As with the general population, treatment of contributing factors including hypothyroidism, vitamin B12 and folate deficiency, and cerebrovascular risk should be considered. Long-term care of FXTAS is complex and requires a multidisciplinary approach.

Studies of premutation carriers report a broad range of other medical problems,[6] commonly including thyroid problems and mood and anxiety disorders. These should be treated as they would be in the general population, acknowledging the additional stressors associated with providing care for someone with special needs. As is the case for anxiety and mood disorders in the general population, clinicians need to take particular care not to attribute valid concerns, for example, about a child, to symptoms of psychiatric disorder.

WHAT ARE THE IMPLICATIONS FOR FAMILY PLANNING?

Typically, the expansion from premutation to full mutation occurs during maternal meiosis; whereas female premutation carriers may experience expansion to a full mutation in their children, male carriers usually pass on the premutation unchanged. The birth of a child with FXS is often the first indication that the family carries the fragile X premutation, and thus there are implications for both the immediate and wider family.

For the mother with a child with FXS already, there will be a high chance that the premutation will expand again in future pregnancies; children inheriting the faulty gene (1 in 2) are likely to have full-mutation FXS. When members of the extended family are identified as carrying the premutation but who do not have children with FXS, the likelihood of expansion into the full mutation is more variable, depending on a number of factors including specific premutation repeat length in the premutation carrier (the risk of expansion is increased with increasing length). Similarly, for those with premutations identified in other screening programmes, the risk of the repeat expanding is more variable. Contact with genetic counselling will be helpful to consider all available options for family planning, which for some may include prenatal testing or preimplantation genetic diagnosis. This can quite understandably be a very stressful time for families and a cause of considerable strain.

Where an individual is identified as carrying the premutation through extended family screening, this brings its own specific issues and potential stresses, for example, not only the news that a woman may have an affected child but also the finding that ovarian reserve may be reduced because of FXPOI leading to difficulty in achieving a pregnancy.

CONCLUSION

Changes in the FMR1 gene are not only associated with both the fragile X syndrome, but also with a wide range of clinical manifestations in family members carrying the premutation. Clinicians are advised to be vigilant for common comorbidities, allowing early diagnosis, referral, and treatment. The familial nature of these conditions is of importance to general practice.

Provenance

Freely submitted; externally peer reviewed.

Competing interests

The authors have declared no competing interests.

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